## REMARKS/ARGUMENTS

### Status of the Claims

Claims 1-31 are rejected.

Claims 13 and 20-22 are currently amended.

New claims 32-36 have been added.

Claims 1-36 are now pending.

### Objection to the Drawings

The Examiner noted a spelling error in the caption of Fig. 2 and required submission of a corrected drawing sheet. In reply, a replacement sheet containing Fig. 2 with "providone" spelled correctly in the caption is submitted herewith. An annotated sheet is also enclosed showing the change that was made.

### Objection to the Specification

In the Office Action of March 26, 2003, the following informalities were indicated: At page 1, line 2, the filing date should be inserted after "09/748,038." It is said that the abbreviation "GFm~~M~~," used in the caption to Figure 3, does not appear to be defined in the specification. In response, these informalities have been corrected in the foregoing Amendments to the Specification. At page 17, lines 1-2 and page 18, lines 26-27 of the Specification, it is apparent that Sulzer's Growth Factor mixture (BDAP, also known as ProVasc™) is what is meant by "GFm" in the caption to Figure 3.

### Benefit Under 35 U.S.C. § 120 of Priority Filing Date

The Office Action has deemed that the instant claims 1-31 are not entitled under 35 U.S.C. § 120 to the benefit of the filing date of parent application 09/748,038 filed December 22, 2000 ("the '038 application"), published as US 2002/0040004. It is said that certain limitations in the claims are not disclosed in the parent application. Without admitting that such is the case, Applicant has added new claims 32-36 which are clearly supported in their entirety in the '038 application. See, for example, paragraphs 44 and 75 (claim 32); paragraph 50 (claims 33-34); paragraph 56 and Fig. 18 (claim 35); and paragraph 73 (claim 36) of US 2002/0040004. The parenthetic claims refer to relevant claims of the present application. Applicants traverse the assertion in the Office Action that the '038 application does not disclose vinyl pyrrolidone polymers in general, and points to paragraph 44 of US

2002/0040004 as an example. Applicants reserve the right to additionally refute any or all of the assertions against the claim to priority of the '038 application, at Applicants' option.

At least claims 32-34 are also fully supported by the disclosure of 09/173,989 filed October 16, 1998 (now U.S. Patent No. 6,211,157), from which 09/748,038 claims the benefit under 35 U.S.C. § 120. For example, see col. 4, line 62 - col. 5, line 10 (claim 32); and col. 4, lines 31-49 (claims 33-34).

## STATEMENT CONCERNING COMMON OWNERSHIP

**In accordance with 35 U.S.C. § 103(c), and 706.02(l)(1)-(3) MPEP, the Office is requested to take note that the present application and U.S. Patent Application Publication No. 2002/0040004 were, at the time the present invention was made, commonly owned by Sulzer Biologics Inc. (now Centerpulse Biologics Inc.).**

Common ownership of the subject applications is also asserted at page 6, lines 22-25 of the Specification. In view of the common ownership of the present invention and 09/748,038 (US Patent Publication No. 2002/0040004), Applicants respectfully submit that US 2002/0040004 is disqualified as prior art in the present case.

## Rejection of Claims Under 35 U.S.C. § 102(b)

In the Office Action of March 26, 2003, claim 31 stands rejected under 35 U.S.C. § 102(b) as being anticipated by the Chemical Abstract 132:40522x. It is said that the same growth factor, solvent and vinyl pyrrolidone polymer are combined according to the same method steps in the Chemical Abstract as in Applicants' claimed method. It is also said in the Office Action that the bioavailability of the BMP in the Chemical Abstract will inherently be increased to the same extent claimed by Applicants. Sufficient evidence of similarity is deemed by the Office to be present between the method of the Chemical Abstract and Applicants' claimed method to shift the burden to Applicants to show that the claimed method is unobviously different than that of the Chemical Abstract.

In response, Applicants respectfully submit that the present application is entitled to the benefits of the priority applications as established above, and therefore antedates the January 24, 2000 publication date of the Chemical Abstract. For example, parent application 09/173,989 filed October 16, 1998 (issued as U.S. Patent No. 6,211,157) discloses the use of povidone as a carrier for GFm at col. 5, lines 7-8 and 65-67, and col. 6 lines 19-21.

Without waiving the foregoing, and in the alternative or additionally, Applicants traverse this rejection for at least the reason that claim 31 distinguishes over the Chemical Abstract. Claim 31 is currently amended to make explicit that which was originally implicit in claim 31. Currently amended claim 31 recites that the method requires increasing the bioavailability of the growth factor "at a site where soft tissue regeneration in a living subject is desired." It also requires administering the aqueous growth factor-PVP mixture to the site where soft tissue regeneration is desired. By contrast, the Chemical Abstract, which is entitled "Injection of basic fibroblast growth factor and bone morphogenetic protein for osteogenesis stimulation," does not teach a method for regenerating soft tissue and it does not teach administering the mixture to a site where soft tissue regeneration is desired. It is implicit in the osteogenesis stimulation method of the Chemical Abstract that the basic FGF-BMP-PVP mixture is administered at a site where osteogenesis is desired for the purpose of obtaining bone growth. For at least the foregoing reasons, the Chemical Abstract is not prior art with respect to the present application and/or claim 31 clearly distinguishes over the teachings of the Chemical Abstract.

**Rejection of Claims Under 35 U.S.C. § 103(a)**

In the Office Action of March 26, 2003, claims 1-19 and 23-31 are rejected under 35 U.S.C. § 103(a) as being obvious over the article by Mueller et al. (*Swiss. Med. Wkly.* 131:23-25 (2001)). It is said that the Mueller et al. article teaches a bone protein mixture, which includes angiogenic factors such as FGF and TGF-$\beta$, in combination with a 5% solution of povidone. The Office deems that sufficient evidence of similarity is present between the Mueller et al. article's source of bone proteins and Applicants' claimed mixture of growth factors to shift the burden to Applicants to provide evidence that their claimed mixture of growth factors is unobviously different than the Muller et al. article's source of bone proteins.

In reply, Applicants respectfully submit that it is apparent on the face of the Mueller et al. article, and in the instant application's priority documents, that the Mueller et al. article is not prior to the present invention and is likely to be simply a publication of experiments confirming the invention. On page 24, first column, first paragraph, the authors state that the bone protein mixture PROVASC™ was provided for those studies by Sulzer Carbomedics, Austin, Texas. At the time the present invention was made Sulzer Carbomedics was a commonly owned sister company of the present assignee. On page 25, at the end of col. 2, acknowledgement is made of the contribution of John Ranieri, a named inventor in the instant application. Furthermore, in paragraph 75 of the instant

priority application (US 2002/0040004), the combination of bone-derived angiogenic protein (BDAP) and povidone for promoting myocardial angiogenesis is taught. Paragraph 73 of US 2002/0040004 teaches that the combination of factors may act synergistically to promote angiogenesis. This observation is subsequently echoed in the Mueller et al. article at page 25, col. 2, lines 1-3 of the first full paragraph, and strongly suggests derivation. Therefore, it is apparent that the Mueller et al. article is not prior to, and not applicable as a reference against, claims 1-19 and 23-31.

Without waiving the foregoing, Applicants reserve the right to additionally show, at Applicants' option, an earlier date of invention and/or to establish derivation of the pertinent teachings of the Mueller et al. article from a presently named inventor and/or from the priority document(s). For example, it may be shown that the studies reported in the Mueller et al. reference represent at most a use of the present invention by third parties at the request of the present assignee and upon disclosure of the present invention and payment for such studies.

Claims 13-15 and 20-22 stand rejected under 35 U.S.C. § 103(a) as being obvious over the Mueller et al. article, as applied above, in view of US 2002/0040004. The Office Action suggests that it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer the combination of growth factors preferred by US 2002/0040004 in the method of the Mueller et al. article because the Mueller et al. article discloses a preference for a mixture of growth factors because of possible synergy, and US 2002/0040004 discloses a combination of growth factors which can be used for the same purpose and with the same carrier taught by the Mueller et al. article. In reply, Applicants submit that neither US 2002/0040004 nor the Mueller et al. article are available as references against claims 13-15 and 20-22 for at least the same reasons as discussed above.

Claims 1-12 also stand rejected under 35 U.S.C. § 103(a) as being obvious over the Chemical Abstract 132:40522x, as applied to the §102(b) rejection of claim 31, above. While acknowledging that the Chemical Abstract does not teach a molecular weight or solution concentration for its PVP, the Office Action suggests that it would be obvious to one of ordinary skill in the art at the time Applicants' invention was made, to determine a molecular weight and solution concentration for the PVP of the Chemical Abstract because molecular weight and solution concentration are art-recognized result-effective variables which are routinely determined and optimized in the polymer, solution chemistry, and pharmaceutical arts. In the Office Action of March 26, 2003 it is stated at paragraph 9,

> It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine molecular weight and solution concentration for the PVP of the Chemical Abstract because molecular weight and solution concentration are art-recognized result-effective variables which are routinely determined and optimized in the polymer, solution chemistry, and pharmaceutical arts.

In reply, Applicants respectfully traverse for at least the reason that, as acknowledged in the Office Action, the Chemical Abstract teaches injection of basic fibroblast growth factor and bone morphogenetic protein for osteogenesis stimulation. By contrast, Applicants' stated PVP molecular weight range of "about 2.5 kD to about 25 kD" relates to compositions for stimulating angiogenesis. To make the distinction clearer, claim 1 is currently amended to require that the composition is capable of promoting angiogenesis when it is administered to a living subject at a site in need of angiogenesis.

The C.C.P.A. has stated, "...[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller* (220 F.2d 454, 456 (1955). [underlining added] Applicants respectfully submit that in the present case, the general conditions of Applicants' claims, as amended, are not disclosed in the cited reference. For example, PVP molecular weight as a variable parameter, and the requirement for promoting angiogenesis are not disclosed in the Chemical Abstract. Those of skill in the art would recognize that bone growth is quite different than soft tissue growth and/or angiogenesis, and that one could not assume that an optimized parameter for one situation would equally apply in the others, or even that povidone is suitable for use with growth factors outside the bone growth context. More specifically, bone growth requires migration and attachment of a different cell type than is the case in angiogenesis and soft tissue repair. It is implicit in the Chemical Abstract that the "result" against which any result-effective parameter would be evaluated is stimulation of osteogenesis, not angiogenesis. There can be no basis, then, for assuming that optimizing a result-effective variable (*i.e.*, PVP molecular weight) for the purposes disclosed in the Chemical Abstract would necessarily arrive at the same PVP molecular weight range of Applicants' claimed compositions, or even that such variables are meaningful in the soft tissue context. Clearly there is no teaching or suggestion in the Chemical Abstract that would lead one of ordinary skill in the art to the PVP molecular weight range of "about 2.5 kD to about 25 kD," as required in claims 1-12.

The present situation is somewhat analogous to *In Re Antonie*, 559 F.2d 618 (CCPA 1977), in which the court found that recognition of a particular functionality is essential to the obviousness of

conducting experiments to determine the value of the parameter (tank volume ratio) which will maximize treatment capacity. Also, see *In re Yates,* 663 F.2d 1054, 1056, 211 USPQ 1149, 1151 (CCPA 1981). The determination of a specific parameter can be an obvious expedient only when the art appreciates that the parameter is a result effective variable. As discussed above, this has not been shown in the Office Action because no evidence in the prior art has been shown to establish that the molecular weight range of PVP is a result effective variable with respect to osteogenesis, much less with respect to angiogenesis. Applicants respectfully submit that no *prima facie* case of obviousness exists in view of the Chemical Abstract, with respect to claims 1-12.

Claims 13-15 stand rejected under 35 U.S.C. § 103(a) as being obvious over the Chemical Abstract 132:40522x, as applied to claims 1-12, above, and further in view of Poser et al. (U.S. Patent No. 5,290,763). It is said in the Office Action that it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use the osteoinductively active mixtures of proteins taught by Poser et al. in place of the bone morphogenetic protein taught by the Chemical Abstract because the substitution of one known functional equivalent for another is *prima facie* obvious, and because the high osteoinductive activity disclosed by Poser et al. for their protein mixtures (e.g., Example 5) would have led one of ordinary skill in the art to expect a high degree of osteogenesis stimulation when used in the method of the Chemical Abstract.

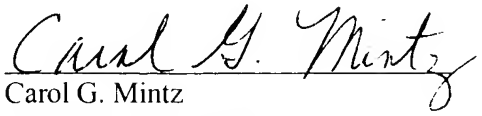
In reply, Applicant submits that even if one were to combine the references as suggested in the Office Action with the expectation of a high degree of osteogenesis, one would still not have the exact same composition of any of claims 13-15 because all of the limitations of currently amended claim 1, from which claims 13-15 depend, are not present in the resulting composition. As discussed above with respect to claim 1, the composition requires PVP having a molecular weight of from about 2.5 kD to about 20 kD. Since there is no teaching or suggestion in either reference that molecular weight is a result-effective variable for stimulating osteogenesis, there is no reason to think that Applicants' claimed molecular weight range of PVP would necessarily result from the teachings of the combined references. For the sake of argument, even if one were to optimize the PVP molecular weight range for stimulating osteogenesis, there would be no assurance that the resulting molecular weight range would be in the claimed range. Moreover, high osteogenic inductive activity is not the same as angiogenesis stimulating activity. For at least these reasons, Applicants submit that claims 13-15 are patentable over the cited references.

**Conclusion**

Applicants respectfully request reconsideration of this application in light of the foregoing amendments and remarks. In the preceding Remarks/Arguments, Applicants may have at times referred to claim limitations in shorthand fashion, or may have focused on a particular claim element. This discussion should not be interpreted to mean that the other limitations can be ignored or dismissed. The claims must be viewed as a whole, and each limitation of the claims must be considered when determining the patentability of the claims. Moreover, it should be understood that there may be other arguments with respect to patentability which have yet to be raised, but which may be raised in the future. For example, Applicants do not waive the right to show, at their option, an earlier date of invention than discussed herein with respect to any reference, and/or to establish derivation of that reference from a present inventor and/or from the priority document(s). This is believed to be a full complete response to each and every ground of rejection and objection raised in the Office Action of March 26, 2003. If Applicants have incompletely addressed any item, an opportunity to supplement this Response is respectfully requested. The format of this Amendment and Response to Office Action is believed to conform with the Revised Amendment Practice as described in "Changes To Implement Electronic Maintenance of Official Patent Application Records," 68 Fed. Reg. 38611 (June 30, 2003).

All of the pending claims are believed to be free of the prior art, and reconsideration and withdrawal of the rejections are respectfully requested. If a telephone conference would facilitate the resolution of this matter, the Examiner is invited to telephone the undersigned representative. Should any fees have been inadvertently omitted, or if any additional fees are required or have been overpaid, please appropriately charge or credit those fees to Deposit Account Number 03-2769 of Conley Rose, P.C., Houston, Texas, and consider this a petition for any necessary extension of time.

Respectfully submitted,



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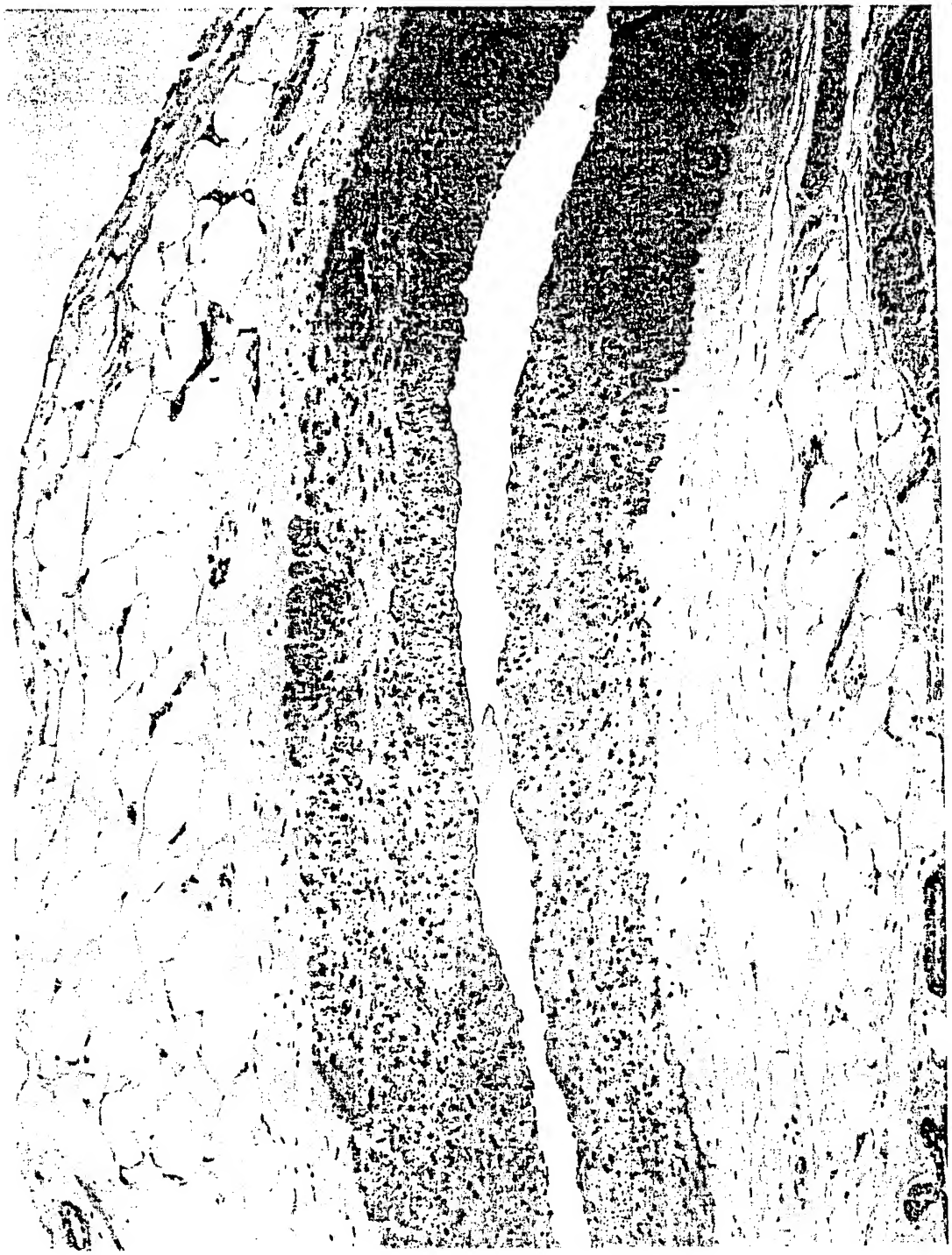

**FIG. 2:** 109-6-5M: Immunostaining of Smooth muscle cells and BrdU positive cells in sections of ischemic myocardium treated with GDF-5 solubilized in 1% povodone.